**REMARKS / ARGUMENTS**

Upon entry of this amendment, the claims pending are claims 1, 4-7, 9, 10, 12-15 and 21-23.

Claims 2, 3, 8, 11 and 16-20 stand cancelled by previous amendments, without prejudice. Claim 1 is amended to clarify the claimed invention by providing as a feature of its antisense sequences that the size of the antisense sequence is between 17 and 50 nucleobases. Claim 1 is further amended to clarify the claimed invention by providing that the antisense sequence fully hybridize, e.g., 100%, with the target. Claims 22 and 23 are added to add further features defining the minimum number of nucleobases that fall within the scope of Claim 1. These amendments are supported by the specification, which demonstrates primer sequences which meet Applicants' definition of antisense of 17 and 19 nucleobases in length (see page 84, lines 22, SEQ ID NO: 4; and page 83, line 29, SEQ ID NO: 7), as well as a large number of examples of 20-mer antisense sequences in Table 1, which are fully, e.g., 100% complementary to the target sequence.

Any subject matter canceled from the claims by amendment is reserved for refiling in a continuation application filed during the pendency of this application. Applicants further affirm the correctness of the inventive entity in view of the cancellation of the claims.

Amendments to the specification are made to correct obvious grammatical or typographical errors and to correctly use trademarks.

No new matter was added by these amendments, which are supported in the original specification.

Claim Rejections based on 35 USC §102(b)

(a) Claims 1, 4-7, 9, 10, 12, 13, 14 and 15 are rejected under 35 USC §102(b) as being allegedly anticipated by International Published Patent Application No. WO 99/67378 (Damha).

The examiner asserts that Damha discloses an oligonucleotide sequence with 15 residues fully complementary to residues 4501-4515 and 5207-5221 of SEQ ID NO: 3. The oligo meets all structural limitations of the claims. Applicants have the obligation to prove that this product does not possess the characteristics of the claims.

Applicants respectfully request reconsideration and withdrawal of these grounds for rejection in view of the above amendments to the claims and the following remarks.

As amended, Claim 1 requires as a feature of its antisense oligonucleotides that the size of the antisense sequence be between 17 and 50 nucleobases and Claims 22 and 23 add the features 19-50 nucleobases or 20-50 nucleobases. These size features of the claims are amply supported by the specification at pages 83-87, which identifies examples of a 17-mer sequence, a 19-mer sequence and numerous 20-mer antisense sequences. Further the minimum number of 17, 19 or 20 oligonucleotides used to define the sequences of the claims are not the same as the 15 residue sequence cited by the Examiner in Damha.

Based on this amendment, Damha cannot be used as a novelty reference against the presently amended claim 1, nor any of the claims dependent therefrom.

This rejection may be properly withdrawn.

(b) Claims 1, 4-6, 10, 12, 13, 14, 15 and 21 are rejected under 35 USC §102(b) as being allegedly anticipated by International Published Patent Application No. WO 96/18736 (Beigelman).

> The examiner states that Biegelman discloses ribozymes wherein the hybridizing region comprises a sequence fully complementary to residues 1404-1417 of SEQ ID NO: 3. The oligo meets all structural limitations of the claims. Applicants have the obligation to prove that this product does not possess the characteristics of the claims.

Applicants respectfully request reconsideration and withdrawal of these grounds for rejection in view of the above amendments to the claims and the following remarks.

As amended, Claim 1 and its dependent claims require as a feature of the antisense oligonucleotides that the antisense sequences fully hybridize, e.g., 100%, with the target. The amendment is supported by the specification, which demonstrates a large number of examples of 20-mer antisense sequences in Table 1, which are fully, e.g., 100%, complementary to the target sequence.

In contrast, Biegelman's ribozyme sequence which contains a hybridizing sequence of 14 nucleotides and **non-hybridizing** sequences, does not meet this required feature of the amended claims.

Based on this amendment, Biegelman cannot be used as a novelty reference against the presently amended claim 1, nor any of the claims dependent therefrom.

This rejection may be properly withdrawn.

Claim Rejections based on 35 USC §103(a)

> Claims 1, 4-7, 9, 10, 12-15 and 21 are rejected under 35 USC §103(a) as being allegedly obvious over International Published Patent Application No. WO 00/09754 (Stenn), in view of Milner et al, **1997** *Nat. Biotech., 15*:537-541 (Milner) and US Patent No. 5,801,154 (Baracchini).
>
> The examiner states that one skilled in the art would have been motivated to modify the vector expressing an antisense oligo targeted to a nucleic acid encoding human stearoyl CoA desaturase, as taught by Stenn, about 8-50 nb as taught by

> Baracchini, modify the antisense compositions, and formulate them into compositions as taught by Baracchini. Further the examiner states that methods of screening for antisense to a known gene was routine as taught by Milner, and that decreasing expression of a target gene by at least 10 is not a high level of inhibition. Stenn provides a *reasonable expectation that screening will provide agents that inhibit by greater than 50%* and provides a vector-expressed antisense sequence. Therefore according to the examiner, *the person of skill would have been expected to find synthetic antisense that inhibits to that degree and that such is not merely an obvious to try standard.* (Italics added)

Applicants respectfully request reconsideration and withdrawal of this rejection in view of the above amendments to the claims and the following remarks.

Applicants respectfully disagree with the examiner's above-italicized contention. Applicants submit that no such expectation is provided. The combined references do not provide any basis for a reasonable expectation that screening will provide agents that inhibit **stearoyl-CoA desaturase** by greater than 50%. The person of skill would **not** be able to **expect** to find synthetic antisense that inhibit **stearoyl-CoA desaturase** to that degree. The combination of the above-cited three references fails to make a *prima facie* case of obviousness against the pending claims of this application.

Stenn is the only reference that discusses human stearoyl CoA desaturase of the three references cited. Yet it says *nothing* about antisense sequences and provides no basis from which one of skill in the art could expect to inhibit synthesis of the desaturase enzyme by any percentage.

The remaining two cited secondary documents teach nothing regarding human stearoyl CoA desaturase. When added to Stenn, they do not support the Examiner's above-noted contention. For example, Baracchini provides

evidence in a test of 16 antisense compounds that **one** antisense compound inhibited expression of the multidrug resistance-associated protein (MRP) by at greater than 30%; and that **another** oligo inhibited at greater than 95% (see col 11, lines 1-9). Baracchini further states that five other antisense compounds inhibit MRP, but does not provide any levels of inhibition (see col. 12, lines 30-34). No further inhibition data is provided for any of the other oligonucleotides listed.

Milner refers to oligonucleotide scanning arrays and tests for inhibition of the expression of **rabbit β-globin protein**. Milner states that at levels of specific inhibition, one 16-mer antisense BG1 inhibited the target "completely"; one 17-mer antisense BG2 inhibited the target by 36%, and the third 15-mer antisense sequence BG3 produced no specific inhibition of target expression. See Milner, page 539, col 1, lines 7-17.

Applicants respectfully submit that

(a) Milner's evidence that three antisense oligos to **rabbit β-globin protein** can inhibit expression of its target 0%, 36% and 100%; plus

(b) Baracchini's evidence that antisense oligos to **human multidrug resistance protein** produced one oligo that inhibits 95%, one that inhibits 36% and five that inhibit at some unidentified percentage; plus

(c) Stenn's lack of any information about antisense to **human stearoyl CoA desaturase,**

do **not** support any expectation as to a level of inhibition that may be anticipated for antisense sequences to **human stearoyl CoA desaturase**. In fact, this combination could as readily suggest to one of skill in the art that for individual targets there can be **no**

preconceived 'expectation of success' that certain levels of inhibition will be achieved by antisense sequences. The Examiner's combination of prior art, when the teachings are taken *as a whole*, does not provide any *suggestion* of the antisense sequences encompassed by Applicants' amended claims and fails to supply both the motivation and a reasonable expectation of success required to set forth obviousness of the pending claims.

Only Applicants have shown antisense sequences to stearoyl CoA desaturase. Only Applicants have shown antisense seuqences that inhibit this target at 10% or greater. Only Applicants have shown assays for testing such targets in its specification.

In view of the above amendments and these remarks, Applicants' respectfully request that the examiner withdraw the outstanding rejections and permit the above pending claims to pass to issue in due course.

The Director is hereby authorized to charge any additional fees required with the filing of this paper or credit any overpayment in any fees to our deposit account number 08-3040.

Respectfully submitted,

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